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FILE 'HOME' ENTERED AT 17:50:16 ON 31 AUG 2000

=> b medline biosis lifesci uspatfull embase

| COST IN U.S. DOLLARS | SINCE FILE
ENTRY | TOTAL
SESSION |
|----------------------|---------------------|------------------|
| FULL ESTIMATED COST | 0.15 | 0.15 |

FILE 'MEDLINE' ENTERED AT 17:50:36 ON 31 AUG 2000

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=> s mibepradil

L1 1209 MIBEPRADIL

=> s l1 and pancrea?

L2 11 L1 AND PANCREA?

=> dup rem 12

PROCESSING COMPLETED FOR L2

L3 7 DUP REM L2 (4 DUPLICATES REMOVED)

=> d 13 ibib abs tot

L3 ANSWER 1 OF 7 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000196389 EMBASE
TITLE: Mycophenolate mofetil decreases endothelial prostaglandin E2 in response to allogeneic T cells or cytokines.
AUTHOR: Blaheta R.A.; Nelson K.; Oppermann E.; Leckel K.; Harder S.; Cinatl J.; Weber S.; Shipkova M.; Encke A.; Markus B.H.
CORPORATE SOURCE: R.A. Blaheta, J.W. Goethe University Hospital, Department of General Surgery, Transplant Immunology Laboratory, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany.
blaheta@em.uni-frankfurt.de
SOURCE: Transplantation, (15 May 2000) 69/9 (1977-1981).
Refs: 16
ISSN: 0041-1337 CODEN: TRPLAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 009 Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background. Prostaglandin E2 (PGE2) is a powerful endogenous immune suppressant and interferes with various T-cell functions. However, it is not known in detail whether immunosuppressive drugs influence the PGE2-driven immune response in transplant patients. Therefore, we investigated the effect of several immunosuppressive compounds, in particular the novel drug mycophenolate mofetil (MMF), on endothelial PGE2 release. Methods. Endothelial cells (HUVEC) were activated by either allogeneic CD4+ or CD8+ T cells, or by the cytokines interleukin-1 or gamma.-interferon. Using an enzyme-linked immunosorbent assay, we analyzed PGE2 release of the activated HUVEC in the presence of MMF, cyclosporine, or tacrolimus. As verapamil and mibepradil also possess immunosuppressive properties, they were included in the study as well. Results. Activation of HUVEC with interleukin-1 or T cells resulted in a drastic accumulation of PGE2 in the supernatant. Cyclosporine or tacrolimus had no effect on PGE2 release. However, Ca2+ channel blockers, when applied at higher dosages, caused a significant increase in PGE2. Interestingly, MMF strongly diminished the PGE2 level in the cell culture supernatant in a concentration-dependent manner. Conclusion. The results demonstrate an inhibitory effect of MMF on PGE2 production, which may

lower the benefits of the PGE2-triggered immune response after organ transplantation.

L3 ANSWER 2 OF 7 MEDLINE
ACCESSION NUMBER: 2000153648 MEDLINE
DOCUMENT NUMBER: 20153648
TITLE: A **mibepradil** metabolite is a potent intracellular blocker of L-type Ca(2+) currents in **pancreatic** beta-cells.
AUTHOR: Wu S; Zhang M; Vest P A; Bhattacharjee A; Liu L; Li M
CORPORATE SOURCE: Department of Pharmacology, University of South Alabama, College of Medicine, Mobile, Alabama, USA.
CONTRACT NUMBER: DK50151 (NIDDK)
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2000 Mar) 292 (3) 939-43.
Journal code: JP3. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY WEEK: 20000504
AB It has been shown that **mibepradil** (Ro 40-5967) exerts a selective inhibitory effect on T-type Ca(2+) currents, although at higher concentrations it can antagonize high voltage-activated Ca(2+) currents. The action of **mibepradil** on Ca(2+) channels is use- and steady-state-dependent and the binding site of **mibepradil** on L-type Ca(2+) channels is different from that of dihydropyridines. By using conventional whole-cell and perforated patch-clamp techniques, we showed that **mibepradil** has an inhibitory effect on both T- and L-type Ca(2+) currents in insulin-secreting cells. However, the effect on L-type Ca(2+) currents was time-dependent and poorly reversible in perforated patch-clamp experiments. By using mass spectrometry, we demonstrated that **mibepradil** accumulates inside cells, and furthermore, a metabolite of **mibepradil** was detected. Intracellular application of this metabolite selectively blocked the L-type Ca(2+) current, whereas **mibepradil** exerted no effect. This study demonstrates that **mibepradil** permeates into cells and is hydrolyzed to a metabolite that blocks L-type Ca(2+) channels specifically by acting at the inner side of the channel.

DUPPLICATE 1

L3 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:306022 BIOSIS
DOCUMENT NUMBER: PREV200000306022
TITLE: A **mibepradil** metabolite is a potent intracellular blocker of L-type Ca²⁺ currents in **pancreatic** beta-cells.
AUTHOR(S): Wu, S.; Zhang, M.; Vest, P. A.; Bhattacharjee, A.; Liu, L.; Li, M.
SOURCE: FASEB Journal, (March 15, 2000) Vol. 14, No. 4, pp. A110. print.
Meeting Info.: Annual Meeting of Professional Research Scientists: Experimental Biology 2000 San Diego, California, USA April 15-18, 2000 Federation of American Societies for Experimental Biology . ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
L3 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:306023 BIOSIS
DOCUMENT NUMBER: PREV200000306023
TITLE: L-type calcium currents are involved in rat islet beta-cell

AUTHOR(S): proliferation.
Zhang, M.; Li, M.
SOURCE: FA
Journal, (March 15, 2000) Vol. 24, No. 4, pp. A110.
print.
Meeting Info.: Annual Meeting of Professional Research
Scientists: Experimental Biology 2000 San Diego,
California, USA April 15-18, 2000 Federation of American
Societies for Experimental Biology
. ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L3 ANSWER 5 OF 7 USPATFULL
ACCESSION NUMBER: 1998:98932 USPATFULL
TITLE: DHA-pharmaceutical agent conjugates of taxanes
INVENTOR(S): Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
PATENT ASSIGNEE(S): Neuromedica, Inc., Conshohocken, PA, United States
(U.S. corporation)

| | NUMBER | DATE |
|--|--|--------------|
| PATENT INFORMATION: | US 5795909 | 19980818 |
| APPLICATION INFO.: | US 1996-651312 | 19960522 (8) |
| DOCUMENT TYPE: | Utility | |
| PRIMARY EXAMINER: | Jarvis, William R. A. | |
| LEGAL REPRESENTATIVE: | Wolf, Greenfield & Sacks, P.C. | |
| NUMBER OF CLAIMS: | 12 | |
| EXEMPLARY CLAIM: | 1 | |
| NUMBER OF DRAWINGS: | 27 Drawing Figure(s); 14 Drawing Page(s) | |
| LINE COUNT: | 2451 | |
| CAS INDEXING IS AVAILABLE FOR THIS PATENT. | | |

AB The invention provides conjugates of cis-docosahexanoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 6 OF 7 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998217007 MEDLINE
DOCUMENT NUMBER: 98217007
TITLE: Different effects of calcium antagonists on fluid filtration of large arteries and albumin permeability in spontaneously hypertensive rats.
AUTHOR: Lacolley P; Poitevin P; Koen R; Levy B I
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, U337, Paris, France.
SOURCE: JOURNAL OF HYPERTENSION, (1998 Mar) 16 (3) 349-55.
Journal code: IEW. ISSN: 0263-6352.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
AB OBJECTIVE: To compare the effects of chronic administration of two dihydropyridines, nifedipine and amlodipine, and the non-dihydropyridine Ca²⁺ antagonist **mibepradil** on fluid filtration of large arteries and extravasation of albumin in spontaneously hypertensive rats. METHODS: Spontaneously hypertensive rats aged 2 months were randomly allocated to oral treatment once a day with 30 mg/kg **mibepradil** (n=12), 100 mg/kg nifedipine (n=12), 20 mg/kg amlodipine (n=12) or placebo (n=12) for 1 month. Instantaneous blood pressure of rats under pentobarbital anaesthesia was recorded at the end of the treatment Fluid filtration

across the carotid arterial wall was determined *in situ* in the isolated carotid artery. Extravasation of 25 mg/kg Evans Blue dye that had been injected intravenously was used to assess whole vascular permeability to albumin after chronic treatment with **mibepradil**. RESULTS:

Similar reductions in mean arterial pressure were obtained in all Ca²⁺ antagonist-treated rats. Heart rate was similar in rats in control, nifedipine and amlodipine groups but was significantly lower in **mibepradil**-treated rats (by 19%, P < 0.001). Fluid filtration across the carotid wall was greater in all Ca²⁺ antagonist-treated animals. However, fluid filtration was significantly less in **mibepradil**-treated rats than it was in nifedipine-treated, and amlodipine-treated rats. Furthermore, administration of **mibepradil** did not significantly modify extravasation of albumin in all tested tissues (**pancreas**, testis, spleen, lung, kidney, intestine, liver, skeletal muscle) except for cardiac and brain tissues, in which

the

permeability of albumin was increased by 24 and 33%, respectively, compared with values for the control group (P < 0.05). CONCLUSION: These results indicate that Ca²⁺ antagonists increase fluid filtration through large arteries from spontaneously hypertensive rats. That the lower fluid filtration in **mibepradil**-treated rats was associated with no change in extravasation of albumin in most tissues and especially in skeletal muscle suggests that vascular permeability in hypertensive rats was impaired less by **mibepradil** treatment than it was by dihydropyridine Ca²⁺ antagonist treatments.

L3 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1997:308651 BIOSIS

DOCUMENT NUMBER: PREV199799616454

TITLE: Chronic T-type Ca-2+ channel blockade with **mibepradil** in hyperinsulinemic, insulin-resistant and hypertensive rats.

AUTHOR(S): Verma, Subodh; Bhanot, Sanjay; Hicke, Alan; McNeill, John H. (1)

CORPORATE SOURCE: (1) Fac. Pharmaceutical Sci., Univ. British Columbia, Vancouver, BC V6T 1Z3 Canada

SOURCE: Cardiovascular Research, (1997) Vol. 34, No. 1, pp. 121-128.

ISSN: 0008-6363.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Objectives: To determine the effects of calcium antagonists on hyperinsulinemia, hypertriglyceridemia and hypertension, we examined the long-term effects of a new calcium channel blocker, **mibepradil**, on plasma insulin levels, plasma triglyceride levels and systolic blood pressure in insulin-resistant and hyperinsulinemic fructose-hypertensive (FH) rats. To this aim, both prevention and reversal protocols were employed. Methods: Prevention study: Male Sprague-Dawley rats were procured at 6 weeks of age and were divided into: control (C, n = 6), control-treated (CT, n = 5), fructose (F, n = 7) and fructose-treated

(FT,

n = 6). Baseline measurements of plasma glucose, insulin and systolic blood pressure were conducted in all groups. At week 7, chronic **mibepradil** treatment (30 mg/kg/day, orally for 6 weeks) was initiated in the CT and FT groups. At week 8, the rats in the F and FT groups were started on a 66% fructose diet to induce hyperinsulinemia and hypertension. Weekly measurements of plasma insulin, plasma triglycerides and systolic blood pressure were conducted for the following 4 weeks. Reversal protocol: In a separate study, 8-week-treated FH rats and their age-matched controls were used to examine the effects of **mibepradil** on reversing fructose-induced hyperinsulinemia and hypertension. Results: The F group exhibited hyperinsulinemia (3.2 ± 0.1 vs. C 2.3 ± 0.07 ng/ml, P < 0.05), hypertension (148 ± 3 vs. C 121 ±

1

mmHg, P < 0.002) and elevated triglyceride levels (5.4 ± 0.8 vs. C 1.6 ± 0.3 mM, P < 0.05). Chronic **mibepradil** treatment prevented

the development of hyperinsulinemia (1.6 ± 0.08 ng/ml, P < 0.004 vs. F) and hypertension (123 ± 1 mmHg, P < 0.001 vs. F) and attenuated the development of hypertriglyceridemia. In the reversal study, **mibefradil** treatment reversed the development of hyperinsulinemia, hypertriglyceridemia and elevated BP in FH rats. Treatment did not affect the plasma glucose levels in any group (prevention or reversal). Conclusions: Long-term treatment with the calcium antagonist, **mibefradil**, both prevents and reverses the development of hyperinsulinemia, hypertriglyceridemia and hypertension in FH rats. These data indicate beneficial effects of **mibefradil** on carbohydrate and lipid metabolism in hyperinsulinemic and insulin-resistant states.

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| FULL ESTIMATED COST | 13.15 | 13.30 |

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|----------------------|------------------|---------------|
| FULL ESTIMATED COST | 13.15 | 13.30 |

=> s (t()type) and (ca or calcium) and channel

L4 2357 (T(W) TYPE) AND (CA OR CALCIUM) AND CHANNEL

=> s 14 and pancrea?

L5 60 L4 AND PANCREA?

=> dup rem 15

PROCESSING COMPLETED FOR L5

L6 30 DUP REM L5 (30 DUPLICATES REMOVED)

=> d 16 ibib abs tot

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| L6 ANSWER 1 OF 30 MEDLINE | DUPLICATE 1 |
| ACCESSION NUMBER: 2000229834 MEDLINE | |
| DOCUMENT NUMBER: 20229834 | |
| TITLE: Functional properties of a new voltage-dependent | |
| calcium channel alpha(2)delta auxiliary | |
| subunit gene (CACNA2D2). | |
| AUTHOR: Gao B; Sekido Y; Maximov A; Saad M; Forgacs E; Latif F; | |
| Wei M H; Lerman M; Lee J H; Perez-Reyes E; Bezprozvanny I; | |
| Minna J D | |
| CORPORATE SOURCE: Hamon Center for Therapeutic Oncology Research, | |
| Departments of Internal Medicine, Pharmacology, University of Texas, | |
| Southwestern Medical Center, Dallas, Texas 75390, USA. | |
| CONTRACT NUMBER: CA71618 (NCI) | |
| P50-CA70907 (NCI) | |
| NS38691 (NINDS) | |
| SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Apr 21) 275 (16) | |
| 12237-42. | |
| Journal code: HIV. ISSN: 0021-9258. | |

PUB. COUNTRY: United States
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-AF040709; GENBANK-AF042792; GENBANK-AF042703;
GENBANK-Z84493; GENBANK-Z75743; GENBANK-Z84494;
GENBANK-Z84495; GENBANK-Z75742; GENBANK-Z84492
ENTRY MONTH: 200007
ENTRY WEEK: 20000702

AB We have positionally cloned and characterized a new **calcium channel** auxiliary subunit, alpha(2)delta-2 (CACNA2D2), which shares 56% amino acid identity with the known alpha(2)delta-1 subunit.

The

gene maps to the critical human tumor suppressor gene region in chromosome

3p21.3, showing very frequent allele loss and occasional homozygous deletions in lung, breast, and other cancers. The tissue distribution of alpha(2)delta-2 expression is different from alpha(2)delta-1, and alpha(2)delta-2 mRNA is most abundantly expressed in lung and testis and well expressed in brain, heart, and **pancreas**. In contrast, alpha(2)delta-1 is expressed predominantly in brain, heart, and skeletal muscle. When co-expressed (via cRNA injections) with alpha(1B) and beta(3)

subunits in Xenopus oocytes, alpha(2)delta-2 increased peak size of the N-type **Ca**(2+) currents 9-fold, and when co-expressed with alpha(1C) or alpha(1G) subunits in Xenopus oocytes increased peak size of L-type channels 2-fold and **T-type** channels 1.8-fold, respectively. Anti-peptide antibodies detect the expression of a 129-kDa alpha(2)delta-2 polypeptide in some but not all lung tumor cells. We conclude that the alpha(2)delta-2 gene encodes a functional auxiliary subunit of voltage-gated **Ca**(2+) channels. Because of its chromosomal location and expression patterns, CACNA2D2 needs to be explored as a potential tumor suppressor gene linking **Ca**(2+) signaling and lung, breast, and other cancer pathogenesis. The homologous location on mouse chromosome 9 is also the site of the mouse neurologic mutant ducky (du), and thus, CACNA2D2 is also a candidate gene for this inherited idiopathic generalized epilepsy syndrome.

L6 ANSWER 2 OF 30 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 2000:238122 BIOSIS

DOCUMENT NUMBER: PREV200000238122

TITLE: Hypermethylation of multiple genes in **pancreatic** adenocarcinoma.

AUTHOR(S): Ueki, Takashi; Toyota, Minoru; Sohn, Taylor; Yeo, Charles J.; Issa, Jean-Pierre J.; Hruban, Ralph H.; Goggins, Michael (1)

CORPORATE SOURCE: (1) Departments of Pathology, Medicine, and Oncology, The Johns Hopkins Hospital, 600 N. Wolfe Street, 632 Ross Building, Baltimore, MD, 21287 USA

SOURCE: Cancer Research, (April 1, 2000) Vol. 60, No. 7, pp. 1835-1839.

ISSN: 0008-5472.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Hypermethylation of CpG islands is a common mechanism by which tumor suppressor genes are inactivated. We studied 45 **pancreatic** carcinomas and 14 normal **pancreata** for aberrant DNA methylation of CpG islands of multiple genes and clones using methylation-specific PCR

(MSP) and bisulfite-modified sequencing. Using MSP, we detected aberrant methylation of at least one locus in 60% of carcinomas. The genes analyzed

included RARBeta (methylated in 20%), p16 (18%), CACNA1G (16%), TIMP-3 (11%), E-cad (7%), THBS1 (7%), hMLH1 (4%), DAP kinase (2%), and MGMT (0%).

In addition, aberrant methylation was found in three CpG islands (MINT31,-1, and -2) in 38, 38, and 14% of carcinomas, respectively. Hypermethylation was largely confined to the carcinomas with only three loci (E-cad, DAP kinase, and MINT2) harboring methylation in some normal pancreata (36, 21, and 14%, respectively). Simultaneous methylation of at least four loci was observed in 5 of 36 (14%) pancreatic adenocarcinomas. We defined this subgroup of pancreatic adenocarcinomas as "CpG island-methylator-phenotype positive (CIMP+)." Two of carcinomas with micro-satellite instability harbored promoter hypermethylation of hMLH1, and both cases were CIMP+. Thus, we conclude that many pancreatic carcinomas hypermethylate a small percentage of genes, whereas a subset displays a CIMP+ phenotype.

L6 ANSWER 3 OF 30 MEDLINE
ACCESSION NUMBER: 2000225542 MEDLINE
DOCUMENT NUMBER: 20225542
TITLE: Neuronal distribution and functional characterization of the **calcium channel** alpha2delta-2 subunit.
AUTHOR: Hobom M; Dai S; Marais E; Lacinova L; Hofmann F; Klugbauer N
CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der Technischen Universitat Munchen, Germany.
SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (2000 Apr) 12 (4) 1217-26.
PUB. COUNTRY: France
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY WEEK: 20000804
AB The auxiliary **calcium channel** alpha2delta subunit comprises a family of three genes, alpha2delta-1 to 3, which are expressed in a tissue-specific manner. alpha2delta-2 mRNA is found in the heart, skeletal muscle, brain, kidney, liver and **pancreas**. We report here for the first time the identification and functional characterization of alpha2delta-2 splice variants and their mRNA distribution in the mouse brain. The splice variants differ in the alpha2 and delta protein by eight and three amino acid residues, respectively, and are differentially expressed in cardiac tissue and human medullary thyroid carcinoma (hMTC) cells. In situ hybridization of mouse brain sections revealed the highest expression of alpha2delta-2 mRNA in the Purkinje cell layer of the cerebellum, habenulae and septal nuclei, and a lower expression in the cerebral cortex, olfactory bulb, thalamic and hypothalamic nuclei, as well as the inferior and superior colliculus. As the in situ data did not suggest a specific colocalization with any alpha1 subunit, coexpression studies of alpha2delta-2 were carried out either with the high-voltage-gated **calcium** channels, alpha1C, alpha1E or alpha1A, or with the low-voltage-gated **calcium channel**, alpha1G. Coexpression of alpha2delta-2 increased the current density, shifted the voltage dependence of **channel** activation and inactivation of alpha1C, alpha1E and alpha1A subunits in a hyperpolarizing direction, and accelerated the decay and shifted the steady-state inactivation of the alpha1G current.

L6 ANSWER 4 OF 30 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000153648 MEDLINE
DOCUMENT NUMBER: 20153648
TITLE: A mibepradil metabolite is a potent intracellular blocker of L-type **Ca(2+)** currents in **pancreatic**

AUTHOR: Wu S; Zhang M; Vest P A; Bhattacharjee A; Liu L; Li M
CORPORATE SOURCE: Department of Pharmacology, University of South Alabama,
College of Medicine, Mobile, Alabama, USA.
CONTRACT NUMBER: DK50151 (NIDDK)
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,
(2000 Mar) 292 (3) 939-43.
Journal code: JP3. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY WEEK: 20000504

AB It has been shown that mibepradil (Ro 40-5967) exerts a selective inhibitory effect on **T-type Ca²⁺** currents, although at higher concentrations it can antagonize high voltage-activated **Ca²⁺** currents. The action of mibepradil on **Ca²⁺** channels is use- and steady-state-dependent and the binding site of mibepradil on L-type **Ca²⁺** channels is different from that of dihydropyridines. By using conventional whole-cell and perforated patch-clamp techniques, we showed that mibepradil has an inhibitory effect on both T- and L-type **Ca²⁺** currents in insulin-secreting cells. However, the effect on L-type **Ca²⁺** currents was time-dependent and poorly reversible in perforated patch-clamp experiments. By using mass spectrometry, we demonstrated that mibepradil accumulates inside cells, and furthermore, a metabolite of mibepradil was detected. Intracellular application of this metabolite selectively blocked the L-type **Ca²⁺** current, whereas mibepradil exerted no effect. This study demonstrates that mibepradil permeates into cells and is hydrolyzed to a metabolite that blocks L-type **Ca²⁺** channels specifically by acting at the inner side of the channel.

L6 ANSWER 5 OF 30 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:154781 BIOSIS
DOCUMENT NUMBER: PREV200000154781
TITLE: High glucose elevated **T-type calcium channel** expression and basal (Ca²⁺)_i in rat islet beta-cells.
AUTHOR(S): Zhang, Min (1)
CORPORATE SOURCE: (1) Pharmacology, University of south Alabama, Mobile, AL, 36688 USA
SOURCE: Biophysical Journal., (Jan., 2000) Vol. 78, No. 1 Part 2, pp. 69A.
Meeting Info.: 44th Annual Meeting of the Biophysical Society. New Orleans, Louisiana, USA February 12-16, 2000
ISSN: 0006-3495.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L6 ANSWER 6 OF 30 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000081696 MEDLINE
DOCUMENT NUMBER: 20081696
TITLE: Cloning of a **T-type Ca²⁺ channel** isoform in insulin-secreting cells.
AUTHOR: Zhuang H; Bhattacharjee A; Hu F; Zhang M; Goswami T; Wang L; Wu S; Berggren P O; Li M
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, University of South Alabama, Mobile 36688, USA.
CONTRACT NUMBER: DK-05151 (NIDDK)
SOURCE: DIABETES, (2000 Jan) 49 (1) 59-64.

JOURNAL CODE: E8X. ISSN: 0012-1797.
PUB. COUNTRY: United States
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
OTHER SOURCE: GENBANK-AF125161
ENTRY MONTH: 200003
ENTRY WEEK: 20000304

AB The **T-type** Ca₂₊ **channel** is an important determinant of electrical activity and of Ca₂₊ influx in rat and human **pancreatic** beta-cells. We have identified and sequenced a cDNA encoding a **T-type** Ca₂₊ **channel** alphal-subunit derived from INS-1, the rat insulin-secreting cell line. The sequence of the cDNA indicates a protein composed of 2,288 amino acids that shares 96.3% identity to alphalG, the neuronal **T-type** Ca₂₊ **channel** subunit. The transmembrane domains of the protein are highly conserved, but the isoform contains three distinct regions and 10 single amino acid substitutions in other regions. Sequencing rat genomic DNA revealed that the alphal-subunit we cloned is an alternative splice isoform of alphalG. By using specific primers and reverse transcription-polymerase chain reaction, we demonstrated that both splice variants are expressed in rat islets. The isoform deduced from INS-1 was also expressed in brain, neonatal heart, and kidney. Functional expression of this alphalG isoform in Xenopus oocytes generated low voltage-activated Ba₂₊ currents. These results provide the molecular biological basis for studies of function of **T-type** Ca₂₊ channels in beta-cells, which is where these channels may play critical roles in diabetes.

L6 ANSWER 7 OF 30 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:254520 BIOSIS
DOCUMENT NUMBER: PREV200000254520
TITLE: High concordance between DNA methylation of tumor suppressor loci in **pancreatic** cancer cell lines and their corresponding primary carcinoma.
AUTHOR(S): Ueki, Takashi (1); Toyota, Minoru (1); Walter, Kimberly M. (1); Jaffee, Elizabeth (1); Yeo, Charles J. (1); Hruban, Ralph H. (1); Goggins, Michael (1)
CORPORATE SOURCE: (1) The Johns Hopkins Med Institutions, Baltimore, MD USA
SOURCE: Gastroenterology, (April, 2000) Vol. 118, No. 4 Suppl. 2 Part 1, pp. A46. print..
Meeting Info.: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA May 21-24, 2000 American Gastroenterological Association
. ISSN: 0016-5085.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L6 ANSWER 8 OF 30 USPATFULL
ACCESSION NUMBER: 1999:155724 USPATFULL
TITLE: Anti-angiogenic Compositions and methods for the treatment of arthritis
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S): Angiogenesis Technologies, Inc., Vancouver, Canada
(non-U.S. corporation)

| | NUMBER | DATE |
|---------------------|----------------|--------------|
| PATENT INFORMATION: | US 5994341 | 19991130 |
| APPLICATION INFO.: | US 1995-478914 | 19950607 (8) |

RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

| | NUMBER | DATE |
|-----------------------|---|----------|
| PRIORITY INFORMATION: | WO 1994-CA373 | 19940719 |
| DOCUMENT TYPE: | Utility | |
| PRIMARY EXAMINER: | Kumar, Shailendra | |
| LEGAL REPRESENTATIVE: | Seed & Berry LLP | |
| NUMBER OF CLAIMS: | 8 | |
| EXEMPLARY CLAIM: | 1 | |
| NUMBER OF DRAWINGS: | 129 Drawing Figure(s); 75 Drawing Page(s) | |
| LINE COUNT: | 5044 | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides compositions comprising an anti-angiogenic factor, and a polymeric carrier. Representative examples of anti-angiogenic factors include Anti-Invasive Factor, Retinoic acids and derivatives thereof, and paclitaxel. Also provided are methods for embolizing blood vessels, and eliminating biliary, urethral, esophageal, and tracheal/bronchial obstructions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 9 OF 30 USPATFULL
ACCESSION NUMBER: 1999:37140 USPATFULL
TITLE: Anti-angiogenic compositions and methods of use
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S): Angiotech Pharmaceuticals Inc., Vancouver, Canada
(non-U.S. corporation)

| | NUMBER | DATE |
|-----------------------|--|--------------|
| PATENT INFORMATION: | US 5886026 | 19990323 |
| APPLICATION INFO.: | US 1995-472413 | 19950607 (8) |
| RELATED APPLN. INFO.: | Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned | |

| | NUMBER | DATE |
|-----------------------|---|----------|
| PRIORITY INFORMATION: | WO 1994-CA373 | 19940719 |
| DOCUMENT TYPE: | Utility | |
| PRIMARY EXAMINER: | Kumar, Shailendra | |
| LEGAL REPRESENTATIVE: | Seed and Berry LLP | |
| NUMBER OF CLAIMS: | 6 | |
| EXEMPLARY CLAIM: | 1 | |
| NUMBER OF DRAWINGS: | 130 Drawing Figure(s); 75 Drawing Page(s) | |
| LINE COUNT: | 4997 | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides compositions comprising an anti-angiogenic factor, and a polymeric carrier. Representative examples of anti-angiogenic factors include Anti-Invasive Factor, Retinoic acids and derivatives thereof, and paclitaxel. Also provided are methods for embolizing blood vessels, and eliminating biliary, urethral, esophageal, and tracheal/bronchial obstructions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 10 OF 30 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 199900186400 BIOSIS
DOCUMENT NUMBER: PREV199900186400
TITLE: Cloning of the rat beta-cell **T-type**
calcium channel alpha1 subunit and its
regulation by glucose.
AUTHOR(S): Zhuang, H. (1); Hu, F.; Bhattacharjee, A.; Zhang, M.; Wu,
S.; Berggren, P.-O.; Li, M.
CORPORATE SOURCE: (1) Dept of Pharmacology, University of South Alabama
College of Medicine, Mobile, AL USA
SOURCE: Biophysical Journal, (Jan., 1999) Vol. 76, No. 1 PART 2,
pp. A409.
Meeting Info.: Forty-third Annual Meeting of the
Biophysical Society Baltimore, Maryland, USA February
13-17, 1999
ISSN: 0006-3495.
DOCUMENT TYPE: Conference
LANGUAGE: English

L6 ANSWER 11 OF 30 USPATFULL
ACCESSION NUMBER: 1998:72478 USPATFULL
TITLE: Cell Line for the rapid expression of functional
calcium channels
INVENTOR(S): Offord, James David, Ann Arbor, MI, United States
PATENT ASSIGNEE(S): Warner-Lambert Company, Morris Plains, NJ, United
States (U.S. corporation)

| | NUMBER | DATE |
|--|---|--------------|
| PATENT INFORMATION: | US 5770447 | 19980623 |
| APPLICATION INFO.: | US 1997-923489 | 19970904 (8) |
| RELATED APPLN. INFO.: | Division of Ser. No. US 1995-467203, filed on 6 Jun
1995, now patented, Pat. No. US 5712158 | |
| DOCUMENT TYPE: | Utility | |
| PRIMARY EXAMINER: | Wax, Robert A. | |
| ASSISTANT EXAMINER: | Hobbs, Lisa J. | |
| LEGAL REPRESENTATIVE: | Anderson, Elizabeth M. | |
| NUMBER OF CLAIMS: | 1 | |
| EXEMPLARY CLAIM: | 1 | |
| NUMBER OF DRAWINGS: | 7 Drawing Figure(s); 6 Drawing Page(s) | |
| LINE COUNT: | 267 | |
| CAS INDEXING IS AVAILABLE FOR THIS PATENT. | | |
| AB | The instant invention provides a stable cell line, 34893 2L, for the
rapid functional expression of high voltage activated calcium
channels. | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 12 OF 30 USPATFULL
ACCESSION NUMBER: 1998:14828 USPATFULL
TITLE: Anti-angiogenic compositions and methods of use
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S): Angiogenesis Technologies, Inc., Vancouver, Canada
(non-U.S. corporation)

| | NUMBER | DATE |
|-----------------------|---|--------------|
| PATENT INFORMATION: | US 5716981 | 19980210 |
| APPLICATION INFO.: | US 1995-478203 | 19950607 (8) |
| RELATED APPLN. INFO.: | Division of Ser. No. US 1995-417160, filed on 3 Apr
1995, now abandoned which is a continuation-in-part of
Ser. No. US 1993-94536, filed on 19 Jul 1993, now
abandoned | |

| | NUMBER | DATE |
|--|---|----------|
| PRIORITY INFORMATION: | WO 1994-CA373 | 19940719 |
| DOCUMENT TYPE: | Utility | |
| PRIMARY EXAMINER: | Kumar, Shailendra | |
| LEGAL REPRESENTATIVE: | Seed and Berry LLP | |
| NUMBER OF CLAIMS: | 18 | |
| EXEMPLARY CLAIM: | 1 | |
| NUMBER OF DRAWINGS: | 130 Drawing Figure(s); 75 Drawing Page(s) | |
| LINE COUNT: | 5084 | |
| CAS INDEXING IS AVAILABLE FOR THIS PATENT. | | |
| AB | The present invention provides compositions comprising an anti-angiogenic factor, and a polymeric carrier. Representative examples of anti-angiogenic factors include Anti-Invasive Factor, Retinoic acids and derivatives thereof, and paclitaxel. Also provided are methods for embolizing blood vessels, and eliminating biliary, urethral, esophageal, and tracheal/bronchial obstructions. | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | |
|---------------------|---|
| L6 ANSWER 13 OF 30 | USPATFULL |
| ACCESSION NUMBER: | 1998:9388 USPATFULL |
| TITLE: | Cell line for the rapid expression of functional calcium channels |
| INVENTOR(S): | Offord, James David, Ann Arbor, MI, United States |
| PATENT ASSIGNEE(S): | Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation) |

| | NUMBER | DATE |
|--|--|--------------|
| PATENT INFORMATION: | US 5712158 | 19980127 |
| APPLICATION INFO.: | US 1995-467203 | 19950606 (8) |
| DOCUMENT TYPE: | Utility | |
| PRIMARY EXAMINER: | Wax, Robert A. | |
| ASSISTANT EXAMINER: | Hobbs, Lisa J. | |
| NUMBER OF CLAIMS: | 1 | |
| EXEMPLARY CLAIM: | 1 | |
| NUMBER OF DRAWINGS: | 7 Drawing Figure(s); 6 Drawing Page(s) | |
| LINE COUNT: | 256 | |
| CAS INDEXING IS AVAILABLE FOR THIS PATENT. | | |
| AB | The instant invention provides a stable cell line, 34893 2L, for the rapid functional expression of high voltage activated calcium channels. | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | | |
|--------------------|---|--------------|
| L6 ANSWER 14 OF 30 | BIOSIS COPYRIGHT 2000 BIOSIS | DUPPLICATE 4 |
| ACCESSION NUMBER: | 1998:441460 BIOSIS | |
| DOCUMENT NUMBER: | PREV199800441460 | |
| TITLE: | omega-Phonetoxin-IIA: A calcium channel blocker from the spider Phoneutria nigriventer. | |
| AUTHOR(S): | Cassola, Antonio Carlos (1); Jaffe, Howard; Fales, Henry M.; Afeche, Solange Castro; Magnoli, Fabio; Cipolla-Neto, Jose | |
| CORPORATE SOURCE: | (1) Dep. Physiol. Biophysics, Inst. Biomed. Sci., Univ. Sao Paulo, Av. Lineu Prestes 1524, Sao Paulo, SP 05508-900 Brazil | |
| SOURCE: | Pfluegers Archiv European Journal of Physiology, (Sept., 1998) Vol. 436, No. 4, pp. 545-552. | |
| | ISSN: 0031-6768. | |
| DOCUMENT TYPE: | Article | |
| LANGUAGE: | English | |

AB A peptide with neurotoxic effect on mammals, purified from the venom of the spider *Phoneutria nigriventer*, was studied regarding its primary structure and its effects on voltage-gated **calcium** channels. The peptide, named omega-phonetoxin-IIA, has 76 amino acids residues, with 14 Cys forming 7 disulphide bonds, and a molecular weight of 8362.7 Da. The neurotoxicity is a consequence of the peptide's blocking effects on high-voltage-activated (HVA) **calcium** channels. N-type HVA **calcium** channels of rat dorsal root ganglion neurons are blocked with affinity in the sub-nanomolar concentration range. The toxin also blocks L-type channels of rat beta **pancreatic** cells, with an affinity 40 times lower. Although not studied in detail, evidence indicates that the toxin also blocks other types of HVA **calcium** channels, such as P and Q. No effect was observed on low-voltage activated, **T-type calcium** channels. The significant homologies between omega-phonetoxin-IIA and the peptides of the omega-agatoxin-III family, and the overlapping inhibitory effects on **calcium** channels are discussed in terms of the structure-activity relationship.

L6 ANSWER 15 OF 30 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1999:204479 BIOSIS

DOCUMENT NUMBER: PREV199900204479

TITLE: Effect of cholecystokinin on cytosolic Ca²⁺ dynamics in rat

pancreatic B cells.

AUTHOR(S): Kimura, Hiroyuki (1)

CORPORATE SOURCE: (1) Department of Physiology, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, 060-0818 Japan

SOURCE: Japanese Journal of Veterinary Research, (Nov., 1998) Vol. 46, No. 2-3, pp. 129-130.

ISSN: 0047-1917.

DOCUMENT TYPE: Article

LANGUAGE: English

L6 ANSWER 16 OF 30 MEDLINE

DUPPLICATE 5

ACCESSION NUMBER: 1998231527 MEDLINE

DOCUMENT NUMBER: 98231527

TITLE: Voltage dependent **calcium** channels in adrenal glomerulosa cells and in insulin producing cells.

AUTHOR: Horvath A; Szabadkai G; Varnai P; Aranyi T; Wollheim C B; Spat A; Enyedi P

CORPORATE SOURCE: Department of Physiology and Laboratory of Cellular and Molecular Physiology, Semmelweis University of Medicine, Budapest, Hungary.

SOURCE: CELL CALCIUM, (1998 Jan) 23 (1) 33-42.
Journal code: CQE. ISSN: 0143-4160.

PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199808

AB We have examined the structure and function of Ca²⁺ channels in excitable endocrine cell types, in rat adrenal glomerulosa cells and in two insulin producing cell types, the rat **pancreatic** beta cell and the INS-1 cell line. In previous studies on glomerulosa cells, we observed low (**T-type**) and high threshold (L-type) voltage dependent Ca²⁺ currents in addition to a K⁺ induced inward rectifying Ca²⁺ current (I_{gl}). beta cells are known to exhibit T-, L- and N-type currents. We have

now found that INS-1 cells also show low threshold (**T-type**) and high threshold Ca²⁺ currents. The latter was further resolved by organic inhibitors into L-type and P/Q-type currents and no I_{gl} was detected. The expression of the pore-forming alpha 1 subunit of voltage dependent Ca²⁺ channels was studied by means of reverse transcription-polymerase chain reaction (RT-PCR), followed by restriction enzyme mapping and/or sequencing. Both in glomerulosa and

pancreatic beta cells, the neuroendocrine (D) class of the alpha 1 subunit, known to be responsible for L-type current, represents the majority of the P_{Ca} product. Comparable amounts of the neuroendocrine (D) and the neuronal A-type alpha 1 subunits dominate the message in INS-1 cells. Different characteristics of Ca²⁺ currents in these cell types is discussed in view of the **channel repertoire**.

L6 ANSWER 17 OF 30 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97253484 EMBASE
DOCUMENT NUMBER: 1997253484
TITLE: **T-type calcium** channels facilitate insulin secretion by enhancing general excitability in the insulin-secreting .beta.-cell line, INS-1.
AUTHOR: Bhattacharjee A.; Whitehurst R.M. Jr.; Zhang M.; Wang L.; Li M.
CORPORATE SOURCE: Dr. M. Li, Department of Pharmacology, University of South Alabama, College of Medicine, Mobile, AL 36688, United States. mli@jaguar1.usouthal.edu
SOURCE: Endocrinology, (1997) 138/9 (3735-3740).
Refs: 42
ISSN: 0013-7227 CODEN: ENDOAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The present study addresses the function of **T-type** voltage-gated **calcium** channels in insulin-secreting cells. We used whole-cell voltage and current recordings, capacitance measurements, and RIA techniques to determine the contribution of **T-type calcium** channels in modulation of electrical activity and in stimulus-secretion coupling in a rat insulin secreting cell line, INS- 1. By employing a double pulse protocol in the current-clamp mode, we found that activation of **T-type calcium** channels provided a low threshold depolarizing potential that decreased the latency of onset of action potentials and furthermore increased the frequency of action potentials, both of which are abolished by administration of nickel chloride (NiCl₂), a selective **T-type calcium channel** blocker. Moreover application of high frequency stimulation, as compared with low frequency stimulation, caused a greater change in membrane capacitance (.DELTA.Cm), suggesting higher insulin secretion. We demonstrated that glucose stimulated insulin secretion in INS- 1 is reduced dose dependently by NiCl₂. We conclude that **T-type calcium** channels facilitate insulin secretion by enhancing the general excitability of these cells. In light of the pathological effects of both hypo and hyperinsulinemia, the **T-type calcium channel** may be a therapeutic target.

L6 ANSWER 18 OF 30 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:308651 BIOSIS
DOCUMENT NUMBER: PREV199799616454
TITLE: Chronic **T-type Ca-2+** channel blockade with mibepradil in hyperinsulinemic, insulin-resistant and hypertensive rats.
AUTHOR(S): Verma, Subodh; Bhanot, Sanjay; Hicke, Alan; McNeill, John H. (1)
CORPORATE SOURCE: (1) Fac. Pharmaceutical Sci., Univ. British Columbia, Vancouver, BC V6T 1Z3 Canada
SOURCE: Cardiovascular Research, (1997) Vol. 34, No. 1, pp. 121-128.
ISSN: 0008-6363.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Objectives: To determine the effects of **calcium** antagonists on hyperinsulinemia, hypertriglyceridemia and hypertension, we examined the long-term effects of a new **calcium channel blocker**, mibepradil, on plasma insulin levels, plasma triglyceride levels and systolic blood pressure in insulin-resistant and hyperinsulinemic fructose-hypertensive (FH) rats. To this aim, both prevention and reversal

protocols were employed. Methods: Prevention study: Male Sprague-Dawley rats were procured at 6 weeks of age and were divided into: control (C, n = 6), control-treated (CT, n = 5), fructose (F, n = 7) and fructose-treated (FT, n = 6). Baseline measurements of plasma glucose, insulin and systolic blood pressure were conducted in all groups. At week 7, chronic mibepradil treatment (30 mg/kg/day, orally for 6 weeks) was initiated in the CT and FT groups. At week 8, the rats in the F and FT groups were started on a 66% fructose diet to induce hyperinsulinemia and hypertension. Weekly measurements of plasma insulin, plasma triglycerides and systolic blood pressure were conducted for the following 4 weeks. Reversal protocol: In a separate study, 8-week-treated FH rats and their age-matched controls were used to examine the effects of mibepradil on reversing fructose-induced hyperinsulinemia and hypertension. Results:

The

F group exhibited hyperinsulinemia (3.2 ± 0.1 vs. C 2.3 ± 0.07 ng/ml, P < 0.05), hypertension (148 ± 3 vs. C 121 ± 1 mmHg, P < 0.002) and elevated triglyceride levels (5.4 ± 0.8 vs. C 1.6 ± 0.3 mM, P < 0.05). Chronic mibepradil treatment prevented the development of

hyperinsulinemia

(1.6 ± 0.08 ng/ml, P < 0.004 vs. F) and hypertension (123 ± 1 mmHg, P < 0.001 vs. F) and attenuated the development of hypertriglyceridemia.

In

the reversal study, mibepradil treatment reversed the development of hyperinsulinemia, hypertriglyceridemia and elevated BP in FH rats. Treatment did not affect the plasma glucose levels in any group (prevention or reversal). Conclusions: Long-term treatment with the **calcium** antagonist, mibepradil, both prevents and reverses the development of hyperinsulinemia, hypertriglyceridemia and hypertension in FH rats. These data indicate beneficial effects of mibepradil on carbohydrate and lipid metabolism in hyperinsulinemic and insulin-resistant states.

L6 ANSWER 19 OF 30 MEDLINE

DUPPLICATE 6

ACCESSION NUMBER: 96249412 MEDLINE

DOCUMENT NUMBER: 96249412

TITLE: Alterations in basal and glucose-stimulated voltage-dependent Ca²⁺ **channel** activities in **pancreatic** beta cells of non-insulin-dependent diabetes mellitus GK rats.

AUTHOR: Kato S; Ishida H; Tsuura Y; Tsuji K; Nishimura M; Horie M; Taminato T; Ikebara S; Odaka H; Ikeda I; Okada Y; Seino Y

CORPORATE SOURCE: Department of Metabolism and Clinical Nutrition, Kyoto University Faculty of Medicine, Kyoto, Japan.

SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1996 Jun 1) 97 (11) 2417-25.

Journal code: HS7. ISSN: 0021-9738.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals

ENTRY MONTH: 199609

AB In genetically occurring non-insulin-dependent diabetes mellitus (NIDDM) model rats (GK rats), the activities of L- and **T-type** Ca²⁺ channels in **pancreatic** beta cells are found to be augmented, by measuring the Ba²⁺ currents via these channels using whole-cell patch-clamp technique, while the patterns of the current-voltage curves are indistinguishable. The hyper-responsiveness of insulin secretion to nonglucose depolarizing stimuli observed in NIDDM

beta cells could be the result, therefore, of increased voltage-dependent Ca²⁺ channel activity. Perforated patch-clamp recordings reveal that the augmentation of L-type Ca²⁺ channel activity by glucose is markedly less pronounced in GK beta cells than in control beta cells, while glucose-induced augmentation of T-type Ca²⁺ channel activity is observed neither in the control nor in the GK beta cells. This lack of glucose-induced augmentation of L-type Ca²⁺ channel activity in GK beta cells might be causatively related to the selective impairment of glucose-induced insulin secretion in NIDDM beta cells, in conjunction with an insufficient plasma membrane depolarization due to impaired closure of the ATP-sensitive K⁺ channels caused by the disturbed intracellular glucose metabolism in NIDDM beta cells.

L6 ANSWER 20 OF 30 MEDLINE

DUPLICATE 7

ACCESSION NUMBER: 97081069 MEDLINE

DOCUMENT NUMBER: 97081069

TITLE: Abnormally expressed low-voltage-activated calcium channels in beta-cells from NOD mice and a related clonal cell line.

AUTHOR: Wang L; Bhattacharjee A; Fu J; Li M

CORPORATE SOURCE: Department of Pharmacology, University of South Alabama, College of Medicine, Mobile 36688, USA.

SOURCE: DIABETES, (1996 Dec) 45 (12) 1678-83.
Journal code: E8X. ISSN: 0012-1797.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199703

AB A macroscopic low-voltage-activated (LVA) inward current was found in pancreatic beta-cells isolated from NOD mice. However, this current was not present in nondiabetic prone mouse (e.g., Swiss-Webster) pancreatic beta-cells. We performed pharmacological analyses on this current in NOD insulinoma tumor cells (NIT-1). This cell line was developed from pancreatic beta-cells of a transgenic NOD mouse. The sodium-channel blocker, tetrodotoxin (TTX; 2 micromol/l) had no effect on this LVA current. The amplitudes of currents elicited by a -20 mV test pulse retained similarity when the extracellular sodium concentration was increased from 0 to 115 mmol/l; when the extracellular calcium concentration was decreased from 10 to 2 mmol/l, there was an approximate 50% reduction of this current elicited by a -30 mV test pulse. Neither the L-type calcium-channel blocker, nifedipine (3 micromol/l), nor the N-type calcium-channel blocker, omega-CgTx-GVIA (1 micromol/l), at -30 mV produced an appreciable effect. The T-type calcium-channel blockers, nickel (3 micromol/l) and amiloride (250 micromol/l), effectively reduced the peak of this current. In 2 mmol/l calcium external solution, the threshold of voltage-dependent activation of this calcium current was approximately -65 mV, and the peak current occurred at -20 mV. Half-maximum steady-state inactivation was around -43 mV. The mean time constant of slow deactivating tail currents generated by a preceding 20 mV

pulse was 2.53 ms. The intracellular free calcium concentration was two- to threefold higher in NOD mouse pancreatic beta-cells compared with Swiss-Webster pancreatic beta-cells. We concluded that there are LVA calcium channels abnormally expressed in NOD mouse beta-cells. This LVA calcium channel may be factorial to the high cytosolic free calcium concentration observed in these cells, and thereby may contribute to the pathogenesis of NOD mouse beta-cells.

L6 ANSWER 21 OF 30 MEDLINE

DUPLICATE 8

ACCESSION NUMBER: 97200279 MEDLINE

DOCUMENT NUMBER: 97200279
TITLE: The intrinsic rhythmicity of spike-burst generation in pancreatic beta-cells and intercellular interaction within an islet.
AUTHOR: Kitasato H; Kai R; Ding W G; Omatsu-Kanbe M
CORPORATE SOURCE: Department of Physiology, Shiga University of Medical Science, Ohtsu, Japan.. kitasato@belle.shiga-med.ac.jp
SOURCE: JAPANESE JOURNAL OF PHYSIOLOGY, (1996 Oct) 46 (5) 363-73.
Ref: 71

PUB. COUNTRY: Journal code: KON. ISSN: 0021-521X.
Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199707

ENTRY WEEK: 19970702

AB The **pancreatic** beta-cell has four types of Ca^{2+} channel (L-type, **T-type**, low-threshold slowly inactivating, and low-threshold non-inactivating Ca^{2+}), although the low-threshold non-inactivating Ca^{2+} channel has not yet been confirmed experimentally. Beside these, there are at least three types of K^+ channels ($\text{K}(\text{ATP})$, $\text{K}(\text{Ca}, \text{V})$, and $\text{K}(\text{V})$), and transporters (GLUT-2, $\text{Na}^+/\text{Ca}^{2+}$ -countertransporter, and Na^+/K^+ -pump) as schematically shown in Fig.4. Opinions on the mechanism of spike-burst

are

converging to the following view: At intermediate glucose concentrations, the intracellular ATP/ADP ratio oscillates in the following way. A gradual

rise in the ATP/ADP ratio causes gradual progression of depolarization to the threshold for the low-threshold Ca^{2+} channels, of which the opening causes regenerative depolarization to the plateau potential on which spikes (the L-type Ca^{2+} channel contributes to spike firing) are superimposed. During the active phase, a fall in the ATP/ADP ratio

follows

a gradual rise in ATP consumption. Slight repolarization due to the opening of a small fraction of $\text{K}(\text{ATP})$ channels triggers regenerative repolarization. With the progress of repolarization, a residual fraction of voltage-gated Ca^{2+} channels (low-threshold non-inactivating) are deactivated. During the silent phase, a gradual rise in the ATP/ ADP ratio

leads to gradual depolarization back to the threshold for the next spike-burst. There are still a diversity of views regarding the mechanism of the initial spike-train. On the basis of observations made in various laboratories including ours, we propose the following working model: At low concentrations of glucose, alpha-cells secret glucagon which induces

a

rise in cAMP in beta-cells lodged in the same islet. A rise in cAMP itself

does not activate the enzymes relevant to glycogenolysis, but merely prepares to activate the enzymes. When extracellular glucose increases, Ca^{2+} spikes are elicited. Influxed Ca^{2+} ions, together with cAMP, work to activate the enzymes, resulting in an additional supply of fuel for ATP synthesis. After sometime, the cAMP level falls back to a low level and the additional glucose supply from stored glycogen stops. This reaction sequence may be the mechanism behind the initial spike-train. To substantiate this working model, it may be important to elucidate the dependence of the phosphorylase kinase and glycogenphosphorylase activities

on the Ca^{2+} in beta-cells.

L6 ANSWER 22 OF 30 MEDLINE

DUPPLICATE 9

ACCESSION NUMBER: 95168297 MEDLINE

DOCUMENT NUMBER: 95168297

TITLE: A new hypoglycemic agent, A-4166, inhibits ATP-sensitive

AUTHOR: potassium channels in rat **pancreatic** beta-cells.
CORPORATE SOURCE: Akiyoshi M; Kakei M; Nakazaki M; Tanaka H
Medicine, File # Department of Internal Medicine Faculty of
Kagoshima University, Japan..
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1995 Feb) 268 (2 Pt 1)
E185-93.
PUB. COUNTRY: Journal code: 3U8. ISSN: 0002-9513.
United States
LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505

AB Effects of a new hypoglycemic drug, N-[trans-4-isopropylcyclohexy-carbonyl]-D-phenylalanine (A-4166), on membrane current were investigated using the patch-clamp technique in single **pancreatic** beta-cells isolated from rats. A-4166, at a concentration of 10 microM, depolarized membrane potential of beta-cells and evoked action potentials in the presence of 2.8 mM glucose. The single ATP-sensitive K⁺ **channel** (K-ATP **channel**) current recorded in cell-attached membrane patches was reversibly inhibited by A-4166 (> 0.1 microM) without a change in the single-**channel** conductance of the K-ATP **channel**. Both A-4166 and tolbutamide inhibited the whole cell K-ATP **channel** current with half-maximum inhibition (IC50) of 0.23 and 12.8 microM, respectively (Hill coefficient = 1). In inside-out membrane patches, the IC50 with A-4166 occurred at 4.5 nM, in contrast to 0.7 microM for tolbutamide. A-4166 did not affect L- and T-type Ca²⁺ channels or the time-dependent outward current. We conclude that A-4166 specifically blocks the K-ATP **channel** and that the blockade is more potent than that of tolbutamide. The action of A-4166 underlies the mechanism by which the drug stimulates insulin secretion from beta-cells.

L6 ANSWER 23 OF 30 USPATFULL
ACCESSION NUMBER: 94:93310 USPATFULL
TITLE: Interaction of thermal hysteresis proteins with cells and cell membranes and associated applications
INVENTOR(S): Rubinsky, Boris, Albany, CA, United States
Devries, Arthur L., Urbana, IL, United States
Arav, Amir, Albany, CA, United States
PATENT ASSIGNEE(S): The Regents of the University of California, Alameda, CA, United States (U.S. corporation)

| | NUMBER | DATE |
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| PATENT INFORMATION: | US 5358931 | 19941025 |
| APPLICATION INFO.: | US 1993-4919 | 19930115 (8) |
| RELATED APPLN. INFO.: | Continuation-in-part of Ser. No. US 1992-910151, filed on 16 Jul 1992, now abandoned Ser. No. Ser. No. US 1992-910254, filed on 16 Jul 1992, now abandoned And Ser. No. US 1990-562461, filed on 3 Aug 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-466050, filed on 17 Jan 1990, now abandoned | |
| DOCUMENT TYPE: | Utility | |
| PRIMARY EXAMINER: | Robinson, Douglas W. | |
| ASSISTANT EXAMINER: | Weber, Jon P. | |
| LEGAL REPRESENTATIVE: | Townsend and Townsend Khourie and Crew | |
| NUMBER OF CLAIMS: | 38 | |
| EXEMPLARY CLAIM: | 1 | |
| LINE COUNT: | 2452 | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A newly discovered property of thermal hysteresis proteins is the interaction of these proteins with cell membranes and thus with cells themselves, protecting cells and their membranes from damage which they would otherwise suffer upon exposure to non-physiological conditions

such as temperature abnormalities, including both hyperthermic, hypothermic and sub-freezing temperatures. Improved rates of cell viability are observed over a wide range of concentrations which do not involve ice formation, including temperatures above the freezing range as well as temperatures below the freezing range but in vitrification conditions. Heretofore the only known property of these proteins was their ability to interact with ice crystals. In conditions in which ice crystals are formed, it is further discovered that use of the proteins with human cells at the concentrations in which they naturally occur in the source organisms results in aggravating the injury to the cells rather than reducing it, but that the injury is lessened, and the survival rate improved, by using low concentrations. The proteins thus offer benefits in the preservation and improved viability of cell suspensions, tissues and whole organs. The proteins are further discovered to have the ability to block ion channels in mammalian cell membranes, thereby providing a further utility in the treatment of disease conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 24 OF 30 MEDLINE
DUPLICATE 10
ACCESSION NUMBER: 95058263 MEDLINE
DOCUMENT NUMBER: 95058263
TITLE: Increased calcium-channel currents of pancreatic beta cells in neonatally streptozocin-induced diabetic rats.
AUTHOR: Kato S; Ishida H; Tsuura Y; Okamoto Y; Tsuji K; Horie M; Okada Y; Seino Y
CORPORATE SOURCE: Department of Metabolism and Clinical Nutrition, Kyoto University School of Medicine, Japan.
SOURCE: METABOLISM: CLINICAL AND EXPERIMENTAL, (1994 Nov) 43 (11) 1395-400.
PUB. COUNTRY: Journal code: MUM. ISSN: 0026-0495.
United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
AB Using a whole-cell patch-clamp technique, voltage-dependent Ca⁽²⁺⁾-channel activities were found to be increased in cultured single beta cells isolated from neonatally streptozocin-induced diabetic rats (NSZ rats). The current-voltage relationship and inactivation time course of Ba²⁺ currents via L-type Ca²⁺ channels were indistinguishable between NSZ and control rats. However, the current density observed in NSZ rats was significantly greater than that in control rats. Ba²⁺ currents via T-type Ca²⁺ channels were also found to be enhanced in NSZ beta cells. The insulin-secretory capacity of cultured pancreatic islets in response to a depolarizing stimulus (20 mmol/L arginine or 30 mmol/L KCl) in the presence of 11.1 mmol/L glucose was augmented in NSZ rats, whereas that in response to 11.1 and 16.7 mmol/L glucose alone was significantly reduced. It is concluded that the impaired insulinotropic action of glucose in beta cells in NSZ rats is not due to reduced activity of voltage-dependent Ca²⁺ channels. The fact that insulin secretion induced by a depolarizing stimulus was enhanced in NSZ rats may be related to the augmented activity of the voltage-dependent calcium current found in NSZ beta cells.

L6 ANSWER 25 OF 30 MEDLINE
ACCESSION NUMBER: 94265727 MEDLINE
DOCUMENT NUMBER: 94265727
TITLE: Inactivation of voltage-dependent calcium current
in an insulinoma cell line.
AUTHOR: Marchetti C; Amico C; Podest'a D; Robello M
CORPORATE SOURCE: Istituto di Cibernetica e Biofisica, Consiglio Nazionale

SOURCE: delle Ricerche, Genova, Italy.
EUROPEAN BIOPHYSICS JOURNAL, (1994) 23 (1) 51-8.
Journal code: EHU. ISSN: 0175-7571.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199409

AB We have studied the mechanism of **Ca** current inactivation in the beta-cell line HIT-T15 by conventional and perforated patch recording techniques, using two pulse voltage protocols and a combination of current and tail current measurements. In 5 mM **Ca**, from a holding potential of -80 mV, the maximum current showed a complex time course of inactivation: a relatively fast, double exponential inactivation (τ_{h1} approximately 12 ms and τ_{h2} approximately 60 ms) and a very slowly inactivating component ($\tau_h > 1$ s). The faster component (τ_{h1}) was due to the voltage-dependent inactivation of a low-threshold-activated (LVA), **T-type** current, which deactivates more slowly (τ approximately 3-5 ms) than the other components (τ approximately 0.2-0.3 ms). The intermediate component (τ_{h2}) was due to the **Ca**-dependent inactivation of a portion of the high-threshold-activated (HVA) current. A saturating dose of the dihydropyridine (DHP) nifedipine (10 microM) did not affect the LVA current, but inhibited by 68 +/- 5% the transient, **Ca**-sensitive portion of the HVA current and by 33 +/- 12% the long lasting component. We suggest that three components of the **calcium** current can be resolved in HIT cells and the main target of DHPs is a HVA current, which inactivates faster than the DHP-resistant HVA component and does so primarily through **calcium** influx.

L6 ANSWER 26 OF 30 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 94065622 MEDLINE
DOCUMENT NUMBER: 94065622
TITLE: Ascorbic acid modulation of **calcium** channels in **pancreatic** beta cells.
AUTHOR: Parsey R V; Matteson D R
CORPORATE SOURCE: Department of Biophysics, University of Maryland School of Medicine, Baltimore 21201.
SOURCE: JOURNAL OF GENERAL PHYSIOLOGY, (1993 Sep) 102 (3) 503-23.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403

AB We have studied the effect of ascorbic acid on voltage-dependent **calcium** channels in **pancreatic** beta cells. Using the whole-cell and perforated-patch variants of the patch clamp technique to record **calcium** tail currents, we have shown that the slowly deactivating (SD) **calcium channel**, which is similar to the **T-type channel** in other cells, is inhibited in a voltage-dependent manner by ascorbic acid (AA). The other channels that carry inward current in beta cells, FD **calcium** channels and sodium channels, are unaffected by AA. Ascorbic acid causes a voltage-dependent decrease in the magnitude of the SD **channel** conductance which can be explained by the hypothesis that approximately 50-60% of the channels have their voltage dependence shifted by approximately 62 mV in the depolarizing direction. Thus, ascorbate appears to modify only a fraction of the SD channels. The activation kinetics of the ascorbate-modified channels are slower than control channels in a manner that is consistent with this hypothesis. Deactivation and

inactivation kinetics are unaffected by ascorbate. These effects of ascorbate require metal ions, and it appears that some of the activity of ascorbate is due to a product of its metal catalyzed oxidation, perhaps dehydroascorbate.

L6 ANSWER 27 OF 30 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1993:159625 BIOSIS
DOCUMENT NUMBER: PREV199344078425
TITLE: Two types of calcium channel in isolated human pancreatic beta-cells.
AUTHOR(S): Smith, Paul A.; Quayle, John
CORPORATE SOURCE: Univ. Lab. Physiol., Parks Rd., Oxford OX1 3PT UK
SOURCE: Journal of Physiology (Cambridge), (1993) Vol. 459, No. 0, pp. 238P.
Meeting Info.: Meeting of the Physiological Society
Oxford,
England, UK July 27-29, 1992
ISSN: 0022-3751.
DOCUMENT TYPE: Conference
LANGUAGE: English

L6 ANSWER 28 OF 30 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 91002814 MEDLINE
DOCUMENT NUMBER: 91002814
TITLE: Single-channel recordings of two types of calcium channels in rat pancreatic beta-cells.
AUTHOR: Sala S; Matteson D R
CORPORATE SOURCE: University of Maryland School of Medicine, Department of Biophysics, Baltimore 21201..
CONTRACT NUMBER: DK33212 (NIDDK)
SOURCE: BIOPHYSICAL JOURNAL, (1990 Aug) 58 (2) 567-71.
Journal code: A5S. ISSN: 0006-3495.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101

AB Using the cell-attached configuration of the patch clamp technique, we have identified two different types of Ca channels in rat pancreatic beta-cell membranes. The two channels differ in single channel conductance, voltage dependence, and inactivation properties. The single-channel conductance, measured with 100 mM Ba²⁺ in the pipette, was 21.8 pS for the large channel and 6.4 pS for the small channel. The large-conductance channel is similar to the fast deactivating or L-type Ca channel described in other preparations. It is voltage dependent, has a threshold for activation around -30 mV, and can be activated from a holding potential of -40 mV. On the other hand, the small-conductance Ca channel is similar to the SD or T type Ca channel; it has a lower activation threshold, around -50 mV, and it can be inactivated by holding the membrane potential at

-40

mV.

L6 ANSWER 29 OF 30 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 90196224 MEDLINE
DOCUMENT NUMBER: 90196224
TITLE: Sensitivity to Cd²⁺ but resistance to Ni²⁺ of Ca²⁺ inflow into rat pancreatic islets.
AUTHOR: Plasman P O; Hermann M; Herchuelz A; Lebrun P
CORPORATE SOURCE: Laboratory of Pharmacology, Brussels Free University, School of Medicine, Belgium.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1990 Mar) 258 (3 Pt 1) E529-33.
Journal code: 3U8. ISSN: 0002-9513.

PUB. COUNTRY: United States
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199006
AB The presence of different types [long lasting (L) and transient (T)] of active voltage-operated Ca²⁺ channels in islet cells was investigated by comparing the effects of Cd²⁺, Ni²⁺, and 1,4-dihydropyridines on 45Ca uptake, 45Ca efflux, and insulin release in intact rat **pancreatic** islets. In several other excitable cells the **L-channel** has been shown to be modulated by 1,4-dihydropyridines and Cd²⁺, whereas the **T-channel** was reported to be sensitive to Ni²⁺. Nifedipine and Cd²⁺ inhibited whereas BAY K 8644 enhanced the glucose (11.1, 22.2 mM)-stimulated short-term 45Ca uptake, 45Ca efflux, and insulin release. In contrast, the stimulatory effects of glucose (11.1, 22.2 mM) on 45Ca uptake, 45Ca efflux, and insulin release were unaffected by Ni²⁺. These findings confirm that glucose provokes Ca²⁺ entry mainly by activating voltage-sensitive Ca²⁺ channels of the L-type and suggest that the B-cell plasma membrane is not equipped with active **T-type** Ca²⁺ channels.

L6 ANSWER 30 OF 30 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 90192071 MEDLINE
DOCUMENT NUMBER: 90192071
TITLE: Two types of **Ca channel** in rat **pancreatic** beta-cells.
AUTHOR: Ashcroft F M; Kelly R P; Smith P A
CORPORATE SOURCE: University Laboratory of Physiology, Oxford, UK.
SOURCE: PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (1990
Jan)
415 (4) 504-6.
Journal code: OZX. ISSN: 0031-6768.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199006
AB Ba currents flowing through single **Ca**-channels were recorded from cell-attached patches on rat **pancreatic** beta-cells. Two types of voltage-activated **Ca**-channels were found. The first (**T-type**) had a single **channel** conductance of 8 pS in 100 mM Ba, was activated at a low threshold (around -50mV) and inactivated by holding potentials positive to -40 mV. These properties are similar to those described for **T-type** channels in other preparations. The second type of **Ca-channel** (L-type) had a single **channel** conductance of 20pS in 100 mM Ba, was activated at a higher threshold (greater than -30mV), showed little inactivation during a 250 ms pulse and could be activated from a holding potential of -40mV. The dihydropyridine agonist BAY K 8644 selectively prolonged L-type **Ca-channel** openings. These properties are characteristic of L-type **Ca**-channels.

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